BE 528,076

Job No.: 1505-101271 Ref.: BE528076
Translated from French by the Ralph McElroy Translation Company
910 West Avenue, Austin, Texas 78701 USA

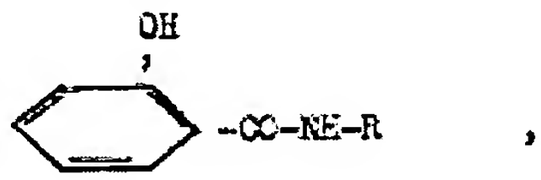
KINGDOM OF BELGIUM
DEPARTMENT OF INDUSTRIAL PROPERTY
PATENT NO. 528076


| | |
|---|---|
| Application filed: | April 13, 1954 at 1:50 p.m. |
| Patent granted: | October 13, 1954 |
| Applicant: | CIBA, INC. Residing in Basel (Switzerland) |
| Priority: | |
| Dates: | April 14, 1953<br>April 29, 1953<br>March 17, 1954 |
| Country: | Switzerland |


# PROCESS FOR PREPARING NEW AMIDES OF CARBOXYLIC ACIDS, COMPOUNDS OBTAINED THEREBY, AND THEIR INDUSTRIAL USE

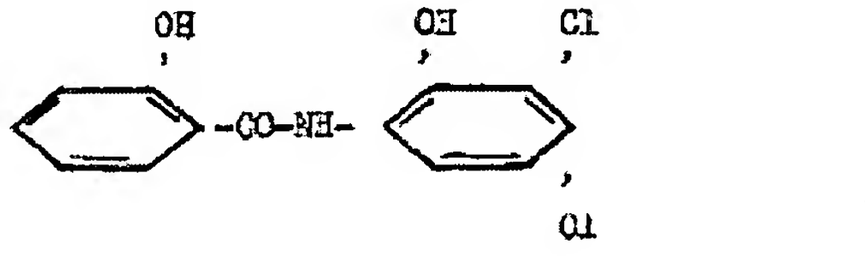

| | |
|---|---|
| Agent: | Parette Law Firm (E. Parette & F. Maes) |
| PRINTED and PUBLISHED: | JANUARY 18, 1957 |


The object of this invention is a process for preparing amides of salicylic acid having the formula:

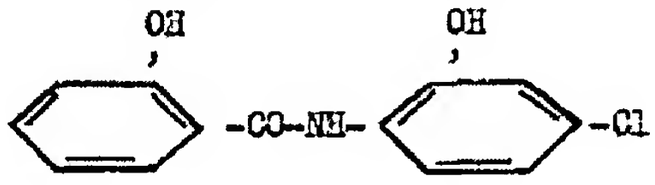



wherein R represents a phenyl radical substituted by at least one atom of halogen, preferably by an atom of chlorine, and having in position 2 a free hydroxy group, as well as their metal salts, such as alkaline and alkaline earth metals, or salts of complex-forming metals such as copper.

In particular, the invention pertains to a process for preparing 2-hydroxy-3,5-dichlorophenylamide of salicylic acid having the formula:



2-hydroxy-4-chlorophenylamide of salicylic acid having the formula:



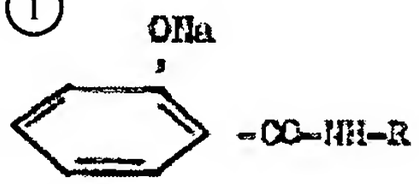
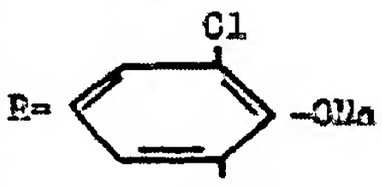
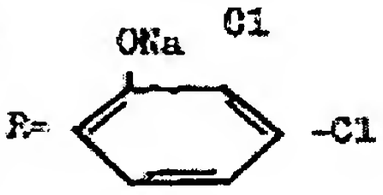
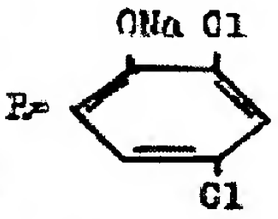

,

and 2-hydroxy-5-chlorophenylamide of salicylic acid, as well as their metal salts, such as their sodium salts.

These new compounds have valuable properties. Among others, they have a strong disinfectant and preservative action, and consequently they have a wide variety of uses as disinfecting and preservation agents. For example, they are appropriate for disinfection of the skin, of instruments, of dressing materials, linens, or similar items, and may also be used to disinfect or preserve foods or fodder, or in the textile industry. They can be used alone or, if desired, mixed with other active or inert substances, in solution or emulsion, for example as ointments, or also in the form of dry powders.

Because of their highly antibacterial and fungicidal properties, these new compounds may also be used as medicines, and can be used, for example, in the form of ointments, particularly for skin diseases caused by pathogenic fungi.

With respect to corresponding compounds in which the hydroxy group of the R radical is lacking or is in position 4 instead of being in position 2, or it is substituted, under the same conditions they have a stronger activity, for example against *Staphylococcus aureus* or *Escherichia coli*, as shown in the following table:

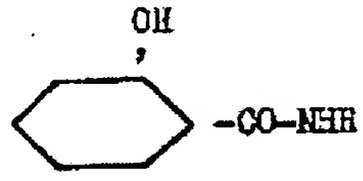
| Composés de formule générale : (1)  | Dilution bactériostatique limite (en g par litre) (2) | | Dilution bactéricide limite (en g par litre) (3) | |
|---|---|---|---|---|
| | Staph. aureus. | E. Coli | Staph. aureus | E. Coli |
|  | 0,01-0,005 | > 1 | > 1 | > 1 |
|  | 0,5 | 0,5 | > 1 | > 1 |
|  | > 0,1 | > 1 | > 1 | > 1 |
|  | 0,005 | 0,05 | 0,05 | 0,1 |
|  | 0,001 | 0,05 | 0,05 | > 1 |

Key: 1 Compounds having the general formula:

2 Bacteriostatic limit dilution (in g per liter)*

3 Bactericidal limit dilution (in g per liter)

These new amides of salicylic acid are obtained by preparing, in a known manner, the carboxylic acid amides having the formula:



wherein R represents a phenyl radical substituted by at least one halogen atom and having, in position 2, a free hydroxy group. In particular, the compounds of formulas R'-X and Y-R" can be made to act on each other. In these compounds, X and Y represent two radicals reacting on each other with formation of the carbamyl group -CO-NH- linking the two phenyl radicals, or by transforming the Z radical into a carbamyl group, in compounds of formula R'-Z-R", in which Z represents a radical that can be transformed into a carbamyl group.

---

* [Note: In table, commas in numerals indicate decimal place.]

In these formulas, R' represents a phenyl radical presenting, in position 2, as the only substituent, a free hydroxy group or a substituent that can be transformed into such a group. R" represents a phenyl radical having, in position 2, a free hydroxy group or a substituent that can be transformed into such a group and, additionally, at least one halogen atom or a substituent that can be transformed into such an atom. In the compounds obtained comprising substituents that can be transformed into free hydroxy groups and/or into halogen atoms, said substituents are then transformed, in any order, into free hydroxy groups or into halogen atoms.

In this way, for example, it is possible to make a carboxylic acid of formula R'-COOH or one of its reactive derivatives, for example, a halide, react with an amine of formula R" -$NH_2$.

On the other hand, it is possible to make a halide, particularly a bromide or iodide with formula R"-Hal, react in the presence of a condensation agent with an amide of formula R'-CO-$NH_2$.

Another embodiment of the process consists of making a ketone of formula R'-CO-R" react with triazoic acid.

A substituent that can be transformed into a free hydroxy group is, for example, an acyloxy group that is transformed by standard hydrolysis. One radical that can be transformed into a halogen atom is, for example, the $NO_2$ group which can be transformed by reduction into an aminogenic group and, by diazotization and Sandmeyer reaction, into a halogen atom.

The reactions indicated are carried out in a known manner in the presence or absence of dilution agents and/or condensation agents and/or catalysts, if necessary by cooling or operating at high temperature, in the open or a closed vessel under pressure. Thus, for example, in the case indicated above of the reaction of an acid with formula R'-COOH with an amine of formula R"-$NH_2$, it is preferable to work in the presence of a dehydrating agent, particularly phosphorus trichloride or thionyl chloride in an anhydrous solvent.

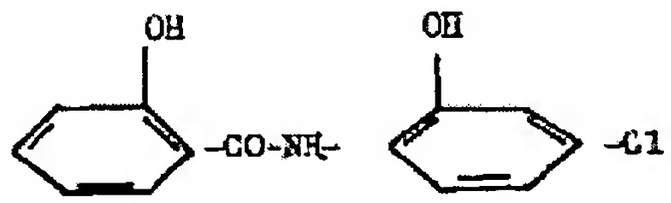
Depending on the process used, we obtain the new compounds of this invention in the form of free phenols or salts thereof. These salts may be transformed into phenols by a standard method. Starting from the latter, it is also possible, for example, by reaction with metal hydroxides or by double decomposition of appropriate salts, to prepare metal salts, for example, alkaline metal salts or the salts obtained with complex-forming metals such as copper.

This invention also concerns, as new industrial products, the products consistent with those obtained by the product defined above.

The invention is described in more detail in the following nonlimiting examples. The ratio between each part by weight and each part by volume is the same as the ratio between one gram and one cubic centimeter. Temperatures are given in degrees centigrade.

Example 1

With agitation and at 50° C, a quantity of 14 parts by weight of phosphorus trichloride is added to a mixture of 34.5 parts by weight of salicylic acid and 36 parts by weight of 2-hydroxy-4-chloraniline in 600 parts by volume of toluene dried on sodium. The reaction mixture is then heated to boiling by reflux with continuing agitation. It is cooled and a quantity of 300 parts by volume of water is added and neutralized with a two normal solution of sodium carbonate. The reaction mixture then undergoes steam distillation. The residue is cooled, and the resulting crystallized reaction product is separated by filtration; it is then washed with water and dried. By using decoloring activated charcoal, the crude reaction product with a light brown color (melting at 161 to 167°C) is recrystallized several times in alcohol, which makes it possible to isolate two different products. The principal product, about 70% of the yield, melts at 180 to 181°C, and the secondary product, which separates first at the time of recrystallization, melts at 153°C. The product with a high melting point is 2-hydroxy-4-chlorophenylamide of salicylic acid, having the formula:



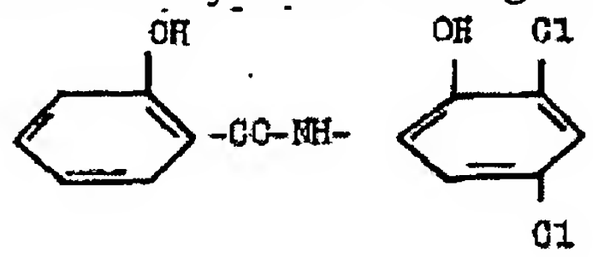

It is recrystallized two more times in glacial acetic acid; it melts at 181.5 to 182°C.

To prepare the sodium salt of this product, a quantity of 10 parts by weight of the above salicylic acid amide is completely dissolved in 130 parts by volume of distilled water and 6.8 parts by volume of a concentrated solution of sodium hydroxide, with slight heating. The solution is then evaporated to dryness under a vacuum. The resulting sodium salt is dissolved in water to yield a clear solution.

Example 2

A mixture of 300 parts by volume of toluene dried on sodium, 28 parts by weight of salicylic acid, and 36.1 parts by weight of 2-hydroxy-3,5-dichloroaniline are heated with agitation to 60°C. Then 11.3 parts by weight of phosphorus trichloride are heated to this temperature and the mixture is heated for a few hours to boiling at reflux. After 300 parts by volume of water are added, the reaction mixture is then cooled and neutralized with a two normal solution of sodium carbonate. The reaction mixture then undergoes steam distillation. The residue is cooled and filtered, and the filtration cake is then washed with water and dried. The resulting crude product is almost colorless and melts at 188 to 195°C. It is recrystallized in absolute methanol using decoloring activated charcoal. In this way we obtain first of all a small quantity of a product with a relatively low melting point, which melts at 142°C. A product that melts at 213 to 214°C then separates as the principal quantity from the concentrated mother

liquors. This product is recrystallized several times in 85% aqueous methanol. The resulting 2-hydroxy-3,5-dichlorophenylamide of salicylic acid having the formula:

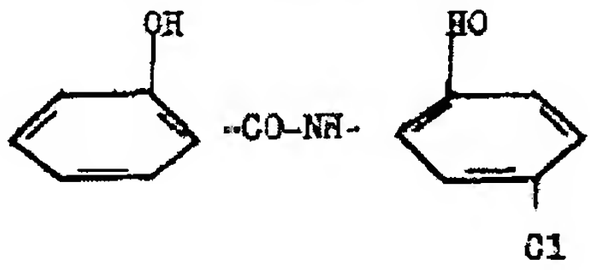



melts at 218.5 to 219°C.

To prepare the sodium salt of this product, 2 parts by weight of the salicylic acid amide indicated above are dissolved hot in 100 parts by volume of distilled water to which 1.35 parts by volume of a concentrated solution of sodium hydroxide have been added. The solution is evaporated under a vacuum until it is dry. The remaining sodium salt is water soluble and yields a clear solution.

Example 3

A quantity of 140 parts by weight of phosphorus trichloride is added gradually, at 50°C and with agitation, to a suspension of 345 parts by weight of salicylic acid and 370 parts by weight of technical grade 2-hydroxy-5-chloraniline (at 97%) in 5000 parts by volume of dry toluene. It is then heated to boiling for an additional 4 h. We add to the mixture 3000 parts by volume of water and 1000 parts by volume of a two normal solution of sodium carbonate, agitate for 1 h and distill the mixture with steam. The distillation residue is isolated on a suction funnel and purified by treatment with methanol and by filtration. This results in separation of an insoluble secondary fraction. The filtrate is evaporated to dryness, the residue is reconstituted in a half-normal solution of sodium hydroxide, the solution is filtered until it is clear and precipitated with hydrochloric acid, and the resulting precipitate is spun dry. Finally, the compound is dissolved in ethanol, the solution is boiled with animal black, and an equal volume of boiling water is added to it. The cold-formed crystals are spun dry and allowed to dry. The resulting 2-hydroxy-5-chlorophenyl amide of salicylic acid having the formula



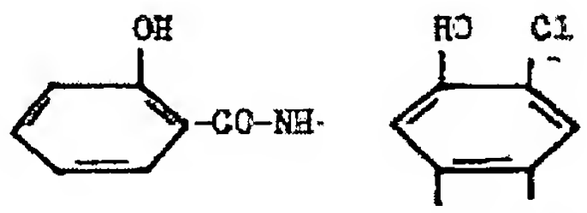

melts at 194 to 194.5°C.

For therapeutic use of this product, it can be introduced in a standard manner in the form of an ointment with the following composition: 2.5% of 2-hydroxy-5-chlorophenylamide of salicylic acid, 31.5% Carbowax 1540, 30% Carbowax 4000, 30% propylene glycol and 6% water.

Example 4

With agitation and at 0°C, a quantity of 700 parts by weight of acetylsalicylic acid chloride dissolved in 1200 parts by volume of absolute ether is added gradually to a solution made up of 1820 parts by weight of technical grade 2-hydroxy-3,5,6-trichloraniline at 83.3% in 550 parts by volume of absolute ether. This is agitated for 2 h at ambient temperature, then for 3 h at 40°C. The reaction product is spun dry and washed by putting it in suspension successively in water, in tenth normal hydrochloric acid, and again in water. It is then dissolved cold in a highly diluted solution of sodium hydroxide, the insoluble fractions are separated, it is precipitated by diluted hydrochloric acid, diluted, and spun dry. For purification, the filtration cake is dissolved in alcohol, the solution is boiled with activated charcoal and filtered, then an equal quantity of boiling water is added while boiling. Crystallization occurs immediately. The product is still impure, and it must be recrystallized a second time in the same way. This yields 340 parts by weight of 2-hydroxy-3,5,6-trichlorophenylamide of acetylsalicylic acid with a melting point of 216.5-217.5°C. After an additional crystallization, the melting point is raised to 217-218°C.

To saponify the acetyl group, 1 part by weight of the acetylated compound is heated for 30 min at 80°C in 20 parts by volume of a half-normal solution of sodium hydroxide, again precipitated hot with diluted hydrochloric acid, which is also hot, and the filtration cake is thoroughly washed with water. It is recrystallized by dissolution in 20 parts by volume of alcohol with the addition to the boiling solution of 10 parts by volume of boiling water. In this way we obtain, with a quantitative yield, 2-hydroxy-3,5,6-trichlorophenylamide of salicylic acid, having the formula:




in the form of small blunted needles with a melting point of 219.5°C to 220°C. When it is recrystallized one more time, the melting point is raised to 221°C.

Example 5

In a period of 40 min, with agitation and at a temperature lower than 5°C, we introduce a solution of 15.5 parts acetylsalicylic acid chloride in 40 parts by volume of absolute ether into a solution of 11 parts by weight of 2-hydroxy-5-nitroaniline in 60 parts by volume of dry pyridine. It is agitated for an additional period of one and 1.5 h at 20 to 25°C, then for 5 h at 50°C. We then eliminate the ether by distillation. The reaction mixture is agitated in 400 parts by volume of

two normal hydrochloric acid; a viscous mass separates immediately. After a few hours, the reaction product solidifies, so that it can be crushed. Afterwards, it is spun dry, washed until it is neutral, and dried.

After recrystallization several times in ethyl acetate, the resulting 2-hydroxy-5-nitrophenylamide of acetylsalicylic acid melts at 248-250°C; it is a crystalline yellow powder.

To split the acetyl group, we hydrolyze 11.7 parts by weight of this amide by boiling them for 2 h at reflux in 480 parts by volume of alcohol and 360 parts by volume of a two normal solution of sodium hydroxide.

When the resulting 2-hydroxy-5-nitrophenylamide of salicylic acid is recrystallized in methanol, it melts and decomposes at 271°C; it is a yellow powder.

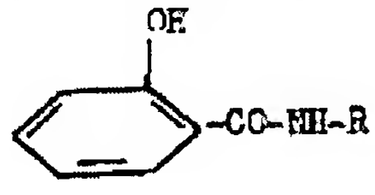
We then hydrogenate the hydrolyzed product in an alcohol solution in the presence of a nickel catalyst under a pressure corresponding to one column of water 2.5 m high. The 2-hydroxy-5-amino-phenylamide of salicylic acid that is formed is diazotated and transformed, in the presence of cuprous chloride and hydrochloric acid following Sandmeyer's method, into 2-hydroxy-5-chlorophenylamide of salicylic acid, which is identical to the reaction product obtained in Example 3. It can be transformed into its water-soluble sodium salt as described in Example 2.

The 2-hydroxy-5-chlorophenylamide of salicylic acid can be used in the technique, for example, in the form of its sodium salt. In this way cellulose materials, such as cotton, can be impregnated with a 0.5% aqueous solution of its sodium salt, which offers good protection against fungal attack.

In addition, the sodium salt can be pressed into tablets with starch, possibly with the use of materials that accelerate dissolution in water, and said tablets may be used as disinfection and preservation agents. By mixing the above-mentioned sodium salt with finely pulverized dilution agents, for example, with urea, powdered cork, or similar agents, we obtain a powder that can be spread readily.

Claims

1. A process for the preparation of new amides of salicylic acid, characterized in that we use a known technique to prepare carboxylic acid amides having the formula:




or metal salts thereof, R representing in the formula indicated a phenyl radical substituted by at least one halogen atom and having a free hydroxy group in position 2.

This invention can also be characterized by the following points:

a) Compounds of formulas R'-X and Y-R" are made to act on one another. In these formulas, X and Y represent two radicals reacting with each other and giving rise to the formation of -CO-NH-carbamyl groups linking the two phenyl radicals; R', a phenyl radical presenting in position 2, as the only substituent, a free hydroxy group of a substituent that can be transformed into such a group; and R", a phenyl radical having in position 2 a free hydroxy group or a substituent that can be transformed into such a group, and additionally at least one halogen atom or a substituent that can be transformed into such an atom. Then, in the resulting compounds having substituents that can be transformed into free hydroxy groups and/or into halogen atoms, said substituents are transformed in any order into free hydroxy groups or into halogen atoms. Then, if desired, the resulting free hydroxylated compounds are transformed into their metal salts, or the resulting metal salts are transformed into free hydroxylated compounds.

b) In the compounds of formula R'-Z-R" where in Z represents a radical that can be transformed into a carbamyl group -CO-NH, R' represents a phenyl radical having, in position 2 as the only substituent, a free hydroxy group or a substituent that can be transformed into such a group, and R" is a phenyl radical having in position 2 a free hydroxy group or a substituent that can be transformed into such a group and, in addition, at least one halogen atom or a substituent that can be transformed into such an atom, we transform the Z radical in the carbamyl group. Then, in any order, in the resulting compounds having substituents that can be transformed into free hydroxy groups and/or into halogen atoms, we transform said substituents into free hydroxy groups or into halogen atoms; then if desired, we transform the resulting free hydroxylated compounds into their metal salts, or the resulting metal salts are transformed into free hydroxylated compounds.

c) As starting substances we use a carboxylic acid with the formula R'-COOH or one of its reactive derivatives, and an amine with the formula R"-$NH_2$, R' and R" having in these formulas the significance indicated in b).

d) Preferably in the presence of a dehydrating agent, salicylic acid is made to react with an amine having the formula R-$NH_2$, wherein R has the significance indicated in 1).

e) Phosphorus trichloride is used as the dehydrating agent.

f) 2-hydroxy-3,5-dichlorophenyl amide of salicylic acid or its metal salts are prepared.

g) 2-hydroxy-4-chlorophenylamide of salicylic acid or its metal salts are prepared.

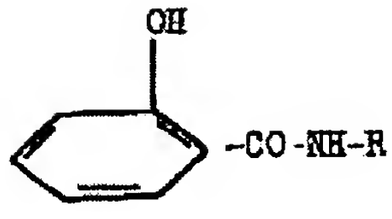
h) 2-hydroxy-5-chlorophenylamide of salicylic acid or its metal salts are prepared.

i) 2-hydroxy-3,5,6-trichlorophenyl amide of salicylic acid or its metal salts are prepared.

2. As new industrial products.

j) The new compounds obtained by the implementation of the process defined in 1).

k) The amides of salicylic acid having the formula:




wherein R represents a phenyl radical substituted by a halogen atom, preferably by a chlorine atom and having, in position 2, a free hydroxy group, as well as their metal salts. The 2-hydroxy-3,5-dichlorophenylamide of salicylic acid and its metal salts.

m) The sodium salt of 2-hydroxy-3,5-dichloro-phenylamide of salicylic acid.

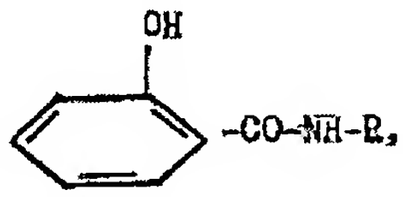
n) The 2-hydroxy-4-chlorophenylamide of salicylic acid and its metal salts.

o) The sodium salt of 2-hydroxy-4-chlorophenyl amide of salicylic acid.

p) The 2-hydroxy-5-chlorophenylamide of salicylic acid and its metal salts.

q) The 2-hydroxy-3,5,6-trichlorophenylamide of salicylic acid and its metal salts.

r) Disinfection or preservation agents, characterized in that they contain amides of salicylic acid, having the formula:




wherein R has the significance given under 1), or metal salts thereof.

s) Disinfection or preservation agents, characterized in that they contain 2-hydroxy-5-chlorophenylamide of salicylic acid or metal salts of this amide.